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Topical review

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Abstract

Background and aims: Bariatric surgery remains a mainstay for treatment of morbid obesity. However, long-term adverse outcomes include chronic abdominal pain and persistent opioid use. The aim of this review was to assess the existing data on prevalence, possible mechanisms, risk factors, and outcomes regarding chronic abdominal pain and persistent opioid use after bariatric surgery.
Methods: PubMed was screened for relevant literature focusing on chronic abdominal pain, persistent opioid use and pharmacokinetic alterations of opioids after bariatric surgery. Relevant papers were cross-referenced to identify publications possibly not located during the ordinary screening.
Results: Evidence regarding general chronic pain status after bariatric surgery is sparse. However, our literature review revealed that abdominal pain was the most prevalent complication to bariatric surgery, presented in 3–61% of subjects with health care contacts or readmissions 1–5 years after surgery. This could be explained by behavioral, anatomical, and/or functional disorders. Persistent opioid use and doses increased after bariatric surgery, and 4–14% initiated a persistent opioid use 1–7 years after the surgery. Persistent opioid use was associated with severe pain symptoms and was most prevalent among subjects with a lower socioeconomic status. Alteration of absorption and distribution after bariatric surgery may impact opioid effects and increase the risk of adverse events and development of addiction. Changes in absorption have been briefly investigated, but the identified alterations could not be separated from alterations caused solely by excessive weight loss, and medication formulation could influence the findings. Subjects with persistent opioid use after bariatric surgery achieved lower weight loss and less metabolic benefits from the surgery. Thus, remission from comorbidities and cost effectiveness following bariatric surgery may be limited in these subjects.
Conclusions: Pain, especially chronic abdominal, and persistent opioid use were found to be prevalent after bariatric surgery. Physiological, anatomical, and pharmacokinetic changes are likely to play a role. However, the risk factors for occurrence of chronic abdominal pain and persistent opioid use have only been scarcely examined as have the possible impact of pain and persistent opioid use on clinical outcomes, and health-care costs. This makes it difficult to design targeted preventive interventions, which can identify subjects at risk and prevent persistent opioid use after bariatric surgery. Future studies could imply pharmacokinetic-, pharmacodynamics-, and physiological-based modelling of pain treatment. More attention to social, physiologic, and psychological factors may be warranted in order to identify specific risk profiles of subjects considered for bariatric surgery in order to tailor and optimize current treatment recommendations for this population.

Keywords: bariatric surgery; chronic pain; abdominal pain; opioids; pharmacokinetics.

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1 Introduction

The World Health Organization has officially declared obesity as a global epidemic. Currently, more than 650 million (13%) adults suffer from obesity, defined as a body mass index (BMI) ≥30, and numbers are increasing rapidly with more subjects falling within both the severe obesity category, defined as BMI ≥35, and the morbidly obesity category, defined as a BMI ≥40 [1–4]. Comorbidities, such as cardiovascular diseases, diabetes mellitus, and musculoskeletal disorders are common amongst subjects with morbid obesity [2, 5]. Additionally, chronic visceral pain is highly represented and a clear association between increasing BMI and chronic pain has been demonstrated possibly caused by a combination of lifestyle and mechanical, chemical, and psychological mediators [6, 7]. Preventive programs for subjects with morbid obesity have been executed, to reduce excessive weight and limit subsequent morbidity. However, even comprehensive lifestyle changes were only associated with intermediate weight loss in most subjects, and many regained weight [7, 8].

Bariatric surgery offers the possibility to retain a large long-term weight loss and minimize associated comorbidities compared to non-surgical options. Therefore, it has been a mainstay of treatment for morbid obesity and severe obesity with coexisting comorbidity for decades [4, 9–11].

2 Bariatric surgery

The three most well-known and commonly performed bariatric surgeries are Roux-En-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (LSG) and laparoscopic adjustable gastric band (LAGD) (Fig. 1). Each procedure has its own advantages and disadvantages, which should be taken into account to ensure the optimal selection of surgery for the individual subjects [12, 13].

2.1 Roux-En-Y gastric bypass

A RYGB creates a small pouch (approx. 30 mL in volume), from the upper region of the stomach, which is connected to the jejunum. The remaining stomach with the adjacent duodenum is connected further down the small intestine, hereby generating a Y-configuration and bypassing orally ingested substances (Fig. 1A). The altered anatomy limits ingestion of large food quantities. Moreover, secretion of gut hormones is minimized, stimulating satiety and suppressing hunger. This imply the main mechanisms explaining the large weight loss after the surgery. Digestion and absorption of calories from fat, carbohydrates and proteins are not significantly affected. However, the hormonal and neural changes have abrupt effects on type 2 diabetes [8, 11, 14].

The RYGB results in the largest long-term weight loss compared to other surgeries [15]; however, vitamin- and mineral deficiency is a common challenge, resulting in severe consequences such as anemia, osteoporosis and neurological disorders [16]. Lifelong supplement consumption and dietary regulations are therefore essential. The RYGB is also a more complex and invasive operation compared to LSG and LAGB, resulting in longer hospitalization and higher complication rates [17]. Nevertheless, it was the most frequently performed bariatric surgery worldwide until 2014, wherefrom it was surpassed by LSG [12, 13, 18].

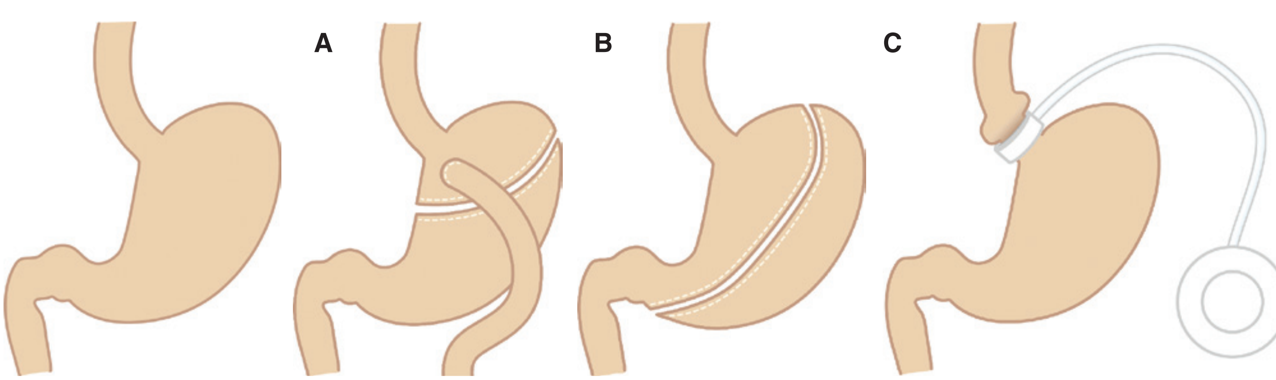

Fig. 1: Illustrations of a normal stomach and the three most common bariatric surgeries. The anatomy of a normal stomach, and the anatomical changes, after; (A) Roux-EN-Y Gastric bypass (RYGB), (B) Laparoscopic Sleeve Gastrectomy (LSG) and (C) Laparoscopic Adjustable Gastric Banding (LAGB).

2.2 Laparoscopic sleeve gastrectomy

During a LSG approximately 80% of the stomach is permanently removed, by creating a tubular pouch (Fig. 1B). Thus, the procedure includes no foreign devices or bypassing of orally ingested substances. Weight loss is achieved due to the reduced gut volume, less production of gastric acids and digestive enzymes, which affects digestion, absorption and the gut hormones with similar outcomes as mentioned for RYGB [17, 19].

2.3 Laparoscopic adjustable gastric band

The LAGB divides the stomach into a smaller upper stomach and a larger lower stomach (Fig. 1C). This procedure is reversible and the band can be adjusted to prompt weight loss or minimize unpleasant side-effects (e.g. nausea). Furthermore, no cutting or resection is performed. Thus, early postoperative complications, malabsorption, and dumping symptoms are rare. On the downside, LAGB is the least effective procedure in obtaining large, long-term weight loss and has the highest rate of re-operation, primarily due to complications caused by the device. Hence, the number of subjects undergoing LAGB is declining and many surgeons abandon this procedure [13, 17].

3 Aim

The aim of this review was to assess the existing data on prevalence, possible mechanisms, risk factors, and outcomes regarding occurrence of chronic abdominal pain and persistent opioid use after bariatric surgery.

4 Methods

The present study is based on three different PubMed searches (http://www.ncbi.nlm.nih.gov/pubmed) from February to May 2019, on the subject "chronic abdominal pain and persistent opioid use after bariatric surgery." The searches included multiple medical subject headings (MeSH) on *bariatric surgery, weight loss, chronic abdominal pain, gastrointestinal symptoms, opioids, pharmacokinetic alterations* and *bioavailability*. Additionally, PubMed was searched using similar free-text word terms on the same topics. Only relevant original articles and reviews published in English were included. Case reports, editorial letters, and reports on symptoms and medication in the early postoperative phase (≤30 days) and articles, which in different manners did not relate to the scope, were excluded. Bibliographies of relevant articles were cross-referenced to identify more articles of interest. There were no restraints for the year of publication.

5 Abdominal pain after bariatric surgery

5.1 Prevalence

Insufficient data exist regarding the development of chronic pain following bariatric surgery, and the actual pain intensity [20]. Excessive weight loss may intensely improve e.g. musculoskeletal pain conditions after bariatric surgery [21]. Results from a survey-based study from Norway indicate that subjects suffering from joint pain decreased from 71% before surgery to 57% 5 years after bariatric surgery [22]. However, subjects may become more vulnerable to chronic pain conditions, due to increased pain sensitivity, decreased pain detection thresholds, and altered pain processing after bariatric surgery [21].

The results from a survey-based study by Gribsholt et al. (2016) demonstrated that the most common symptom, resulting in 34.2% of the health care contacts after RYGB was abdominal pain. The risk was higher among women, young subjects, smokers, unemployed subjects, and subjects with symptoms from previous surgeries [23]. In several studies abdominal pain has been identified as the most common symptom, causing additional health care contacts and hospital readmissions with a prevalence up to 61.4% (Table 1) [8, 22–31]. Chronic abdominal pain was found to be associated with reduced health related quality of life [22]. Even though bariatric surgery is effective for obtaining weight loss and reducing obesity related comorbidity, the number of symptoms, medication use, and health care contacts after surgery continued to be high and represents a significant burden on the subjects as well as upon the society, indicating, that general health conditions are not normalized in these subjects [23, 24, 32]. In general, studies focusing on longitudinal evaluations from before and after bariatric surgery to evaluate the potential casual relationships between bariatric surgery and chronic abdominal pain are lacking. Additionally, evidence is primarily restricted to studies on RYGB surgery, e.g. only one study investigating abdominal pain separate after LSG have been identified in the present review [8, 22–26, 28–30].

Table 1: Prevalence of abdominal pain after bariatric surgery.

Study	Design	Results
Cho et al. [24]	Retrospective study on medical records of subjects undergoing LRYGB surgery at a single hospital admitted to emergency care. $n=733$	The most frequent complaint in the emergency room was abdominal pain, which were presented in 61.4% of the subjects
Saunders et al. [25]	Hospital records for 1-year readmission of subjects undergoing bariatric surgery in a single US hospital setting, for 31 months. $n=1{,}939$	Overall 1-year readmission rate was 18.8%. LAGB had the lowest (12.7%) and RYGB the highest rate (24.2%). Abdominal pain was leading cause of readmission (11.8%)
Gribsholt et al. [23]	Survey on self-reported outcomes (2014) in subjects undergoing RYGB surgery in the Central Region of Denmark 2006–2011. Median follow-up 4.7 years. $n=2{,}238$ undergoing RYGB, $n=89$ controls	63.7% responded the survey. 88.6% reported ≥1 symptoms. 67.6% of subjects were in contact with the healthcare within follow-up, compared to 34.8% controls from the general population. 34.2% of healthcare contacts were caused by abdominal pain
Pernar et al. [26]	Study of subjects who underwent RYGB surgery and were admitted to emergency department (2005–2015). To examine association between clinical parameters and abdominal CT scans. $n=1{,}643$ undergoing RYGB surgery	676 subject visited the emergency department. Abdominal pain was presented in 624 (92%) visitors. No clinical or laboratory parameter were associated with the imaging results
Hogestol et al. [22]	Prospective Norwegian survey on 5-year follow-up of subjects undergoing RYGB surgery. $n=165$	33.8% reported chronic abdominal pain. Among these subjects 48.8% reported indigestion and 29.1%, reported IBS. 18.5% had abdominal pain prior to RYGB
Pierik et al. [27]	Database study in Amsterdam from November 2007 to April 2015 on prevalence and predictive factors of unexplained abdominal pain after bariatric surgery. $n=1{,}788$ subjects underwent LRYGB (1,361) or LSG (118)	Average follow-up was 33.5 months. 21.6% subjects had abdominal pain and 7.4% experienced unexplained abdominal pain after bariatric surgery
Altieri et al. [28]	SPARCS database study on all SG surgeries 2011–2013, including at least 1-year follow-up, for incidence of emergency department visits and hospital readmissions. $n=14{,}080$ subjects who underwent SG surgery	33.9% visited emergency department in follow-up. 53.9% unrelated to surgery. 11.1%, presented with abdominal pain. One-year readmission rate was 12.5%. Readmission causes were 41.7% unrelated to surgery, 8% related, and 3.0% abdominal pain
Blom-Hogestol et al. [29]	Prospective Norwegian survey on random selected subjects undergoing RYGB surgery in a single hospital setting, with 5-year follow-up. $n=234$	71% were readmitted in follow-up, and 97% responded to the survey. Thirty-four percent reported chronic abdominal pain, caused by internal herniation, dumping, food intolerance, gallstones, or IBS. (Same population as Hogestol et al. [22])
Gribsholt et al. [30]	Cohort study on all subjects undergoing RYGB surgery in Denmark 2006–2010, and matched general population controls. Follow-up for median 4.2 years. $n=9{,}985$ undergoing RYGB, $n=247{,}375$ controls	Readmissions in 3.3% subjects undergoing RYGB surgery within 30 days and 23.9% in follow-up. Fifteen percent admitted with abdominal pain. Admission rates before RYGB were 11.5 vs. 5.9 in controls per 100 person-years, increasing to 24.9 vs. 7.1 after surgery
Jakobsen et al. [8]	Cohort in Norwegian outpatient center 2005–2010 and follow-up from 2006 to 2015 Bariatric surgery or specialized medical obesity treatment. $n=932$ surgical (855 RYGB, 69 SG and 8 other), $n=956$ medical treatment	The rate of abdominal pain in subjects undergoing bariatric surgery (26.1%) was higher than in subjects with medical treatment (RR: 1.9, ARD: 12.6% points)
Mala et al. [31]	Review of prevalence, evaluations, etiology, and treatment of abdominal pain specific to RYGB surgery from PubMed searches and clinical experience	Limited evidence suggest about 30% subjects may experience chronic abdominal pain after RYGB, with diverse etiology and undefined cause of pain for a subset of subjects

ARD = absolute risk difference; GI = gastrointestinal; IBS = irritable bowel syndrome; LAGB = laparoscopic adjustable gastric band; LRYGB = laparoscopic Roux-En-Y gastric bypass; LSG = laparoscopic sleeve gastrectomy; n = number of subjects; RYGB = Roux-En-Y gastric bypass; SG = sleeve gastrectomy; US = United States.

5.2 Abdominal pain pathogenesis

The etiologies of abdominal pain after bariatric surgery are diverse, and several causes have been suggested, including; (1) behavioral, dietary disorders such as over- and rapid eating resulting in mechanical distension of the pouch or reduced stomach; (2) functional disorders such as constipation, diarrhea, irritable bowel syndrome and dumping syndrome; (3) biliary disorders such as cholelithiasis, choledocholithiasis or sphincter of oddi dysfunction; (4) pouch or remaining stomach disorders such as peptic ulcer disease, gastro-gastric fistula, gastroesophageal reflux disease and hiatus hernia; (5) small intestine disorders such as abdominal wall and internal hernias [30, 33–35]. However, unfortunately the pain etiology remains undefined in 23–43% of subjects with abdominal pain after RYGB, and the associations after other forms of bariatric surgery are even less evident [28, 30, 34]. Thus, a thorough understanding of the pathogenesis will naturally improve clinical outcomes as mechanism based management can be initiated to prevent chronic abdominal pain after bariatric surgery [28, 33].

5.3 Pharmacological treatment

Symptom improvement on chronic abdominal pain could be obtained from dietary guidance, e.g. if the cause is a behavioral, dietary disorder, whereas in other cases surgery or specific medical treatment is used, e.g. in peptic ulcer. However, in some cases pharmacological pain treatment is needed [26, 28]. The World Health Organizations analgesic ladder was developed for the treatment of cancer pain, but is also used in the treatment of chronic abdominal/visceral pain as there are no treatment guidelines specifically for chronic abdominal pain. Orally administered analgesics are suggested in the following order: non-opioids [non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen]; then weak opioids (e.g. tramadol), on demand; then strong opioids (e.g. morphine), until sufficient pain relief is achieved. Adjuvant analgesics e.g. antidepressants or anticonvulsants, might also provide analgesic effects and could additionally be used to calm fears and anxiety [26, 36].

Acetaminophen is a widely used non-opioid with analgesic and antipyretic effects through central and peripheral non-opioid mechanisms [37]. In contrast to NSAIDs, acetaminophen possesses no clinically relevant anti-inflammatory characteristics. However, it is preferred over NSAIDs, due to its limited gastrointestinal side-effect profile. Acetaminophen treatment is often continued when additional stronger analgesics are needed. Non-opioids are often insufficient for a satisfactory abdominal/visceral pain relief. Thus, opioids are widely used in the management of subjects experiencing severe visceral pain [38]. Opioids produce significant pain relief through direct effects on the visceral pain pathways. However, due to side-effects in the gastrointestinal and central nervous system, it is essential to monitor the subjects closely and manage individual risk-benefit profiles and to prevent development of constipation and addiction. Adjuvant analgesics may be relevant as supplement and have a specific role in the presence of central sensitization or major psychological components [36].

6 Opioid use after bariatric surgery

For decades, efforts to improve general patient-care in the management of chronic pain have triggered an undesirable increase in the number of opioid prescriptions and persistent users [39]. The increased incidence of opioid overprescribing, abuse, misuse, addiction, and overdosing has been an unexpected consequence [7, 39–41]. Sufficient acute multimodal pain management, including opioid treatment, has been found to be an important instrument after any surgery, including bariatric surgery, since this reduces the risk of postoperative chronic pain [42, 43]. However, the efficacy and safety of persistent opioid treatment is controversial [32, 40]. Bariatric surgery is associated with short-term complications, but there are only few studies on long-term outcomes, including long-term opioid use [8, 41].

6.1 Prevalence

Most studies on opioid use after bariatric surgery are based on US insurance-databases or surveys, but European studies have also been published. In general, the results showed that opioid use was common in the subject before bariatric surgery, but increased afterwards (Table 2) [8, 44, 46–49]. In a survey-based study from Michigan it was identified that 21.5% of subjects undergoing bariatric surgery reported to have used opioids the year before surgery and in another US study it was identified that 35.9% used opioids on demand, and 8.0% used opioids persistently, before surgery. Among the persistent users before bariatric surgery, 77.5% continued a persistent use, 19.5% used opioids on demand, whereas only 3.0% reported no opioid use the following year [40, 47]. Contrary, results from

Table 2: Prevalence of persistent opioid use after bariatric surgery.

Study	Design	Results
Raebel et al. [40]	Retrospective US cohort on opioid use 1-year before/after bariatric surgery 2005–2009. Chronic use, defined as ≥10 opioid dispensing over ≥90 days, or dispensing 120-day supply. n = 11,719	Before surgery, 56% used no opioids, 35.9% used opioids on demand, and 8.0% used opioids persistently. Among persistent users, 77.5% continued persistent use, 19.5% used opioids on demand, and 3.0% discontinued opioids 1-year after surgery
Raebel et al. [44]	Retrospective US cohort on opioid use in subjects undergoing bariatric surgery who were non-persistent opioid users 1-year before surgery 2005–2009. Chronic use, defined as ≥10 opioid dispensing over ≥90 days, or dispensing 120-day supply. n = 10,643	4.0% became persistent opioid users 1-year after surgery. Risk factors were pre-surgery analgesics, antianxiety agents, tobacco, and non-laparoscopic band procedures
Tabibian et al. [20]	Retrospective case-control study on opioid records in a pain rehabilitation center 2008–2012. Compare pain treatment outcomes for subjects undergoing bariatric surgery to non-bariatric controls matched on age, gender, and smoking. n = 106 cases, n = 106 controls	Subjects undergoing bariatric surgery used more OME at discharge, than matched non-bariatric subjects with pain. Subjects undergoing bariatric surgery had higher rates of benzodiazepine at discharge (33 vs. 19%) and were less likely to complete treatment (87 vs. 97%). At admission, mean OME was 127.3 mg in cases and 88.3 mg in controls
Brummet et al. [45]	Retrospective US cohort on insurance claims in opioid-naïve subjects undergoing minor and major surgery e.g. bariatric surgery 2013–2014 n = 36,177 subjects undergoing general surgery	Rates of new persistent opioid use were similar in the minor and major surgery groups 5.9–6.5%. >7% subjects were new persistent users after bariatric surgery
King et al. [7]	Survey on longitudinal assessment of opioid use as self-reported daily, weekly, or on demand after Bariatric Surgery in US. n = 2,258	Before surgery, 14.7% used opioids. This decreased to 12.9% after 6 month, but increased to 20.3% after 7 years. 5.8% were new persistent users at 6 month and 14.2% at 7 years. New persistent use was associated with; health insurance, pre-surgery pain, subsequent surgeries, and other analgesic use
Wallén et al. [46]	Retrospective Swedish cohort of the opioid pattern following RYGB in subjects with a high and low opioid consumption pre-surgery. n = 35,612	2.2% of subjects who used <10 mg OME daily before surgery used >10 mg OME daily 2 years after RYGB
Jakobsen et al. [8]	Cohort Norway outpatient center 2005–2010 and follow-up from 2006 to 2015 Bariatric surgery or specialized medical obesity treatment n = 932 surgical (855 RYGB, 69 SG and 8 other), n = 956 medical treatment	New onset of opioid use in subjects undergoing bariatric surgery (19.4%) was higher than after medical treatment (RR: 1.3, ARD: 3.6% points)
Smith et al. [47]	Cohort on new persistent opioid use in subjects undergoing bariatric surgery in Michigan, 2006–2016. Patient-reported survey on opioid use before and at 1 year after surgery. n = 27,799	21.5% used opioids before surgery. 6.3% were new persistent opioid users at 1-year post-surgery. New persistent opioid users lost less weight, had worse psychological wellbeing, body image, and depression, reported less satisfaction by the surgery
Heinberg et al. [21]	Non-systematic review of opioid use after bariatric surgery	Identified four large prospective studies, examining the prevalence of continuing/initiating opioids after bariatric surgery (Raebel et al. [40, 44], Wallén et al. [46], King et al. [7]). The studies indicate that bariatric surgery does not reduce opioid use

ARD = absolute risk difference; n = number of subjects; OME = oral morphine equivalent doses; RR = relative risk; RYGB = Roux-En-Y gastric bypass; SG = sleeve gastrectomy; US = United States.

another study showed a prevalence of 14.7% self-reported opioid users before surgery, which decreased to 12.9% at 6 months after surgery. However, the prevalence of opioid users increased to 20.3% after 7 years [7]. Moreover, the ingested opioid doses was found to increase following bariatric surgery [40, 44, 46]. In a Swedish study it was found, that 2.2% of subjects who used <10 mg oral morphine equivalent daily before surgery used >10 mg oral morphine equivalent daily 2 years after RYGB-surgery [46]. Unfortunately, all the studies lack information on clinical indications for the opioid use [44].

Many subjects initiated a persistent opioid use after bariatric surgery. Raebel et al. (2014) found that 4.0% of non-persistent users before surgery initiated persistent opioid use the year after surgery [44]. In other studies it was identified that >6.3% of subjects, without previous opioid use, initiated persistent opioid use the year after bariatric surgery [45, 47]. Additionally, a study found that 5.8% of subjects without opioid use before bariatric surgery used opioid 6 month after and 14.2% used opioids after 7 years [7]. Studies on opioid use after bariatric surgery, has previously been reviewed, but studies comparing opioid initiation in medical treated controls with morbid obesity were not considered [21]. A cohort-study from Norway compared comorbidity- and medication-changes among subjects with morbid obesity undergoing bariatric surgery or medical treatment. They found, that the absolute risk of initiating persistent opioid use *after* surgical treatment (19.4%) was higher than after medical treatment (relative risk: 1.3, absolute risk difference: 3.6) [8]. Additionally, subjects suffering from chronic pain after bariatric surgery were less likely to complete a pain rehabilitation program, and used higher opioid dose at discharge, than matched non-bariatric subjects with chronic pain at the same pain rehabilitation center [50]. Many of the subjects with persistent opioid use after bariatric surgery, used opioids at least occasionally before surgery [40, 44].

In summary, it is concerning that the prevalence of subjects using opioids increases after bariatric surgery, and that opioid doses seems to increase. This emphasizes the importance of identifying risk of initiating persistent opioid use and of improving specific management of possible chronic pain in subjects undergoing bariatric surgery [32, 44]. Future strategies, for better follow up of subjects after surgery to prevent long-term opioid use, are needed.

6.2 Altered drug pharmacokinetics after bariatric surgery

The anatomical and physiological changes following especially RYGB and LSG impact the pharmacokinetics of some drug classes, potentially leading to therapeutic failure or increased occurrence of side-effects [18, 51, 52]. Especially, the major reduction in gastric volume can affect the rate and extent of absorption after oral administration due to reduced mucosal surface area, altered pH and gastric transit times, which influences disintegration of tablets with pH-sensitive coatings and/or the dissolution of the drug substance [53]. In theory, all four parameters of drug disposition; “absorption, distribution, metabolism and excretion” (ADME), might be affected by the altered gastrointestinal physiology (Fig. 2). However, the effect of the bariatric procedure is difficult to disentangle from the effect of the weight loss [54–56].

In subjects undergoing RYGB, gastrointestinal first-pass metabolism and efflux could be reduced, as cytochrome P450 enzymes and drug transporters expressed in duodenum are bypassed. Additionally, surgery results in shorter intestinal transit times, which limits drug absorption [57–59]. The impact on bile salt solubilisation and lipid degradation of tablets based on lipophilic constituents may be altered in subjects undergoing RYGB. However, results from different studies have shown deviating results with regards to the production and delivery of pancreatic juices containing bile salts and lipases in subjects undergoing bariatric surgery. Furthermore, enterohepatic circulation could potentially be disrupted, affecting absorption of some drug substances [60, 61].

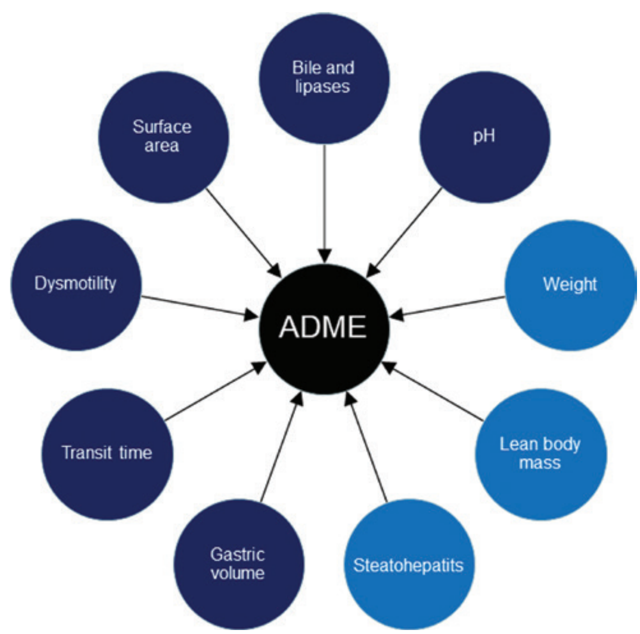

Fig. 2: Factors affecting the pharmacokinetic profile. Different factors could affect the absorption, distribution, metabolism and excretion (ADME) of a given drug. Factors shown in pale blue circles are factors related to the weight loss, and factors shown in dark blue circles are factors related to the altered gastrointestinal physiology induced by the operation. Although the effect of the weight loss may be hard to distinguish from the effect of the surgery, the figure illustrates, many more possible factors to consider than only weight, when a dosing regime is set in a subject who underwent bariatric surgery.

Altered pharmacokinetics is less evident in subjects undergoing LAGB, since the gastrointestinal tract is preserved. However, a large weight loss affects drug distribution, due to decreased lean body mass, and drug metabolism, as steatohepatitis gradually diminishes [54, 55]. Obviously, this mechanism also applies after RYGB and LSG surgery. General pharmacokinetic studies in subjects undergoing RYGB have been reviewed and revealed that 68% of all investigated drugs had increased maximum plasma concentrations (C_{max}) and/or decreased time to maximum plasma concentration (T_{max}) after a RYGB, compared to controls or before surgery. Additionally, 36% of the drugs had increased area under the plasma concentration-time curve after surgery [51]. Thus, the pharmacokinetics of oral administered opioids would be expected to change in subjects undergoing bariatric surgery.

6.3 Pharmacokinetics of opioids after bariatric surgery

To our knowledge, the pharmacokinetics of orally administered opioids in subjects undergoing bariatric surgery, have only been addressed in two studies; both being in subjects undergoing RYGB surgery. Lloret-Linares et al. (2014) studied pharmacokinetics of an oral administered morphine solution before and after RYGB. T_{max} decreased 7.5 times, C_{max} increased 3.3 times and the area under the plasma concentration-time curve was increased 1.6 times 6 months after surgery compared to before surgery [62]. The study lacked a control group, thus changes could be related to weight loss rather than other physiological changes. In another study the pharmacokinetics of a morphine controlled release formulation was investigated in subjects undergoing RYGB surgery and weight-matched controls. No significant difference in any of the studied pharmacokinetic parameters was demonstrated [63]. Thus, the hypothetic pathophysiological changes might not have any significant impact on the pharmacokinetics of morphine for subjects who underwent RYGB surgery.

The pharmacokinetics of orally administered drugs greatly depends on formulation type, physiochemical properties of the drug, lean body mass and type of bariatric surgery. Thus, in order to achieve optimal effect of a drug, dose regulations might be necessary, especially during the first years after surgery [64]. However, the influence of bariatric surgery on the pharmacokinetic fate of drugs is not fully understood and therapeutic failures may occur. Other theories suggest that bariatric surgery may centrally decrease the opioid signaling effect, implying an increased risk of addiction [65]. Future studies aiming at creating clinical decision support tools based on modeling of the pharmacokinetic-pharmacodynamic relationships using physiological-based pharmacokinetic models are warranted in order to optimize medication therapy, including opioids, for this population.

6.4 Adverse events and addiction

A limited number of studies have evaluated adverse effects due to opioid therapy in subjects who underwent bariatric surgery. Increased C_{max} and shorter T_{max} could increase the risk of reaching toxic levels and occurrence of adverse events, especially for drugs with a narrow therapeutic index. Rapid increase in plasma levels of alcohol, hypnotics and narcotics, has been associated with a higher risk of intoxication and addiction [66]. Thus, subjects who underwent bariatric surgery are theoretically at higher risk for adverse events if opioid doses are not adjusted. A higher degree of drowsiness have been reported among subjects who underwent RYGB surgery compared to controls following a controlled release formulation of morphine [63]. Elevating opioid doses could also change pharmacokinetic parameters more drastically in subjects who underwent RYGB surgery depending on the formulation, thus enhancing risks of adverse events [62, 63].

The addictive, euphoric rush is influenced by rapid absorption rates rather than actual opioid concentrations in the central nervous system, hypothetically making subjects undergoing bariatric surgery more prone to addiction. Empirical data have demonstrated a correlation between obesity, overeating and substance abuse [67]. The exact impact of the physiological changes following bariatric surgery remains unclear, but may play a predominant role.

6.5 Risk factors for persistent opioid use

In a few studies the possible risk factors for persistent opioid use after bariatric surgery have been investigated and the results were conflicting [7, 44, 47]. Extraordinary high food consumption, resulting in obesity, may be a coping strategy, related to addictive behavior, and decreased opioid signaling, in some subjects, and bariatric surgery may not address the subjects' underlying psychosocial problems [48, 65, 68]. Subjects with morbid obesity who underwent bariatric surgery may be extra vulnerable to opioid misuse and addiction, because the prevalence of risk factors such as metal health disorders is higher in this population [47, 69]. In a study by

Raebel et al. (2014) it was found that use of opioids, non-opioid analgesics, antianxiety agents, and tobacco before bariatric surgery were associated with persistent opioid use after bariatric surgery. Additionally, they found that persistent opioid use were associated with younger age [44], contrary, in another study an association with older age was identified [47]. New persistent opioid use was also associated with current tobacco use and multi-comorbidity. New persistent opioid users were less likely to be Caucasian, married, or living with a partner [47].

King et al. (2017) further identified multiple risk factors for initiating or continuing opioid use after bariatric surgery, including higher pain-level before surgery, little/no pain improvement, having public health insurance, subsequent surgery, non-opioid analgesic use, and continued benzodiazepine use [7]. In a survey-based study it was found that subjects using low opioid doses just after bariatric surgery required few opioid refills [41]. In general socioeconomic factors and addiction possibly play a role for persistent opioid use [47, 70]. However, more detailed information on sociodemographic factors, comorbidities, medication use, opioid type and formulation in public health-care systems are warranted. An overview of risk factors for persistent opioid use after bariatric surgery are presented in Table 3 [44, 47].

6.6 Clinical outcomes

Postoperative pain management in bariatric surgery is partly based on opioids, since sufficient pain management (with opioids) decrease the risk of chronic postoperative pain [42]. However, regardless of the increasing awareness of possible misuse and related comorbidities in persistent opioid use, the potential impact of persistent opioid use after bariatric surgery, on long-term outcomes such as adverse events, addiction, and comorbidity, is still unknown. In general, persistent opioid users have been found to have lower physical quality of life, compared to the general population [8, 47, 71]. Smith et al. (2018) found that subjects with new persistent opioid use 1 year after bariatric surgery had lower weight loss and metabolic benefits from the surgery, compared to subjects not being persistent opioid users [47]. This could limit remission from obesity related disease. However, this has not yet been investigated. Subjects with new persistent opioid use after bariatric surgery also had worse mental health and reported less satisfaction with the surgery [8, 47]. Raebel et al. (2013) also aimed to determine the association between opioid dose and BMI changes after bariatric surgery, but found no association [40].

New persistent opioid use could be a result of complications following bariatric surgery, resulting in e.g. chronic abdominal pain. Thus, results might be confounded by indication. As earlier stated postoperative pain should not be undertreated. However, it is recommended that guidelines and withdrawal-strategies on proper prescription of opioids after bariatric surgery are followed, in order to limit additional long-term opioid prescribing, without clinical indications [47, 72, 73]. Persistent opioid use after bariatric surgery were associated with some negative outcomes (Fig. 3) [8, 40, 47]. However, more outcomes are to be investigated before appropriateness of persistent opioid use in subjects who underwent bariatric surgery can be determined.

Table 3: Risk factors for persistent opioid users after bariatric surgery.

– Pain before surgery
– Lack of/little pain improvement
– Opioids before surgery (especially high opioid doses)
– Non-opioid analgesic use
– Benzodiazepine use
– Subsequent surgery
– Higher/lower age
– Smoking status
– Ethnicity
– Marital status
– Public health insurance
– No withdrawal plan

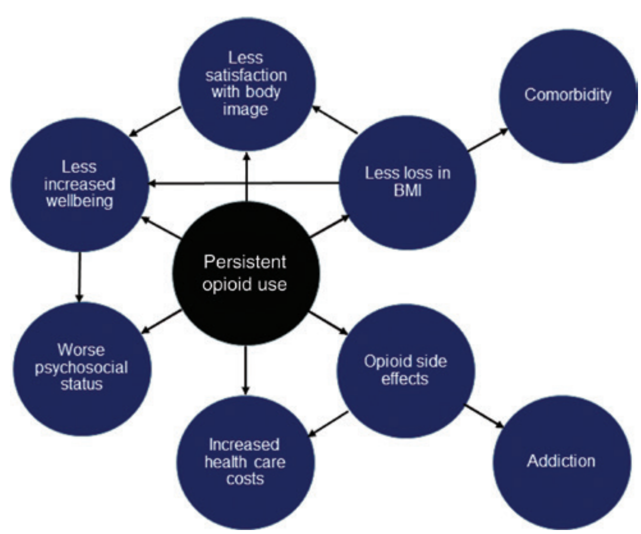

Fig. 3: Outcomes in persistent opioid users after bariatric surgery. Known and expected outcomes from persistent opioid use after bariatric surgery, including possible interactions.

6.7 Economic consequences

Besides the goal of decreased obesity related comorbidity level, bariatric surgery is expected to decrease the long-term health care costs in subjects with morbid obesity. Results from previous studies have proven that bariatric surgery is effective in reducing obesity related comorbidities, which could reduce the health care costs [10, 74]. However, since persistent opioid use following bariatric surgery gave raise to poorer physiological and psychological outcomes [47, 71], possible increased amount of health care system contacts and possible lack of remission or new onset of obesity related comorbidity, suggest that reductions in costs are not obtained in the new persistent opioid users after bariatric surgery [25, 75, 76]. Opioid use before bariatric surgery, or other elective abdominal surgeries, were recently found to be associated with greater overall health care costs both at 90, 180, and 365 days following surgery [49]. However, results on long-term economic outcomes of persistent opioid use *after* bariatric surgery have not yet been investigated and studies must be carried out to advance knowledge within this field.

6.8 Study strengths and limitations

The aim of this review was to assess the existing data on prevalence, possible mechanisms, risk factors, and outcomes regarding occurrence of chronic abdominal pain and persistent opioid use after bariatric surgery. To cover these important clinical problems and the undefined relations multiple structured searches in the most relevant biomedical database (PubMed) were found to be the most appropriate method. The one-database design is a limitation of the present study, in regard of literature coverage. However, the scientific areas were attempted further covered through cross-referencing the included articles.

Unfortunately, the majority of the identified literature in the present study cover populations who had undergone RYGB surgery, indicating, that the existing evidence regarding persistent opioid use and especially abdominal pain after bariatric surgery is lacking in subjects undergoing LSG surgery [22–26, 28, 29]. Two studies identified an overall prevalence on abdominal pain after bariatric surgery including small proportions (7%) of subjects who underwent LSG [8, 30], and only one identified study investigated the prevalence separate in subjects undergoing LSG and found a prevalence of acute abdominal pain between 3 and 11% [27]. This is a limitation in regard of generalization of the chronic abdominal pain status after bariatric surgeries, since clinical outcomes may differ significantly between subjects who have undergone different bariatric procedures. E.g. studies suggest that substance abuse may be more common after RYGB than other bariatric procedures [18, 48, 77]. The absence of sufficient evidence, apply reasons to believe that these complications may not affect subjects in the same extent after undergoing LSG surgery. However, future studies should investigate this issue to clarify the presence of these important clinical problems in the largest population of subjects undergoing bariatric surgery worldwide [18].

7 Conclusion and perspectives

Abdominal pain remains the major cause for health care contacts after bariatric surgery and especially RYGB surgery. Explanations include behavioral, dietary, anatomical, or functional disorders, which may be related to surgery. In general, persistent opioid use is prevalent before bariatric surgery, but the prevalence increases after surgery and higher doses are often used. This could be triggered by chronic pain symptoms, although socioeconomic factors also affect whether subjects discontinue the opioid use. Theories on altered opioid absorption after bariatric surgery are still to be addressed and are of most importance as opioids are widely used in this population. Unfortunately, important factors as weight loss, metabolic benefits, and thus, remission from obesity related comorbidities and achievement of the health economic benefits following bariatric surgery may be limited in subjects with persistent opioid use after bariatric surgery.

Future studies aiming at creating clinical decision support tools based on recognition of social, physiological, and psychological circumstances and modeling of the pharmacokinetic-pharmacodynamic-relationships seems to be warranted, in order to identify subjects at risk for persistent opioid use and optimize the treatment for this population, to minimize side-effects and optimize pain relief.

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